APPLICATION OF THERAPEUTIC ULTRASOUND IN KNEE OSTEOARTHRITIS: AN INTEGRATIVE REVIEW OF RANDOMIZED CLINICAL TRIALS.

Abstract:

Knee osteoarthritis is a leading cause of pain and disability, and therapeutic ultrasound is a widely used electrophysical agent for its conservative management. This integrative review synthesizes randomized controlled trials (2020–2026), retrieved from PubMed, SciELO, Google Scholar and PEDro, on continuous, low-intensity pulsed (LIPUS), phonophoretic and focused therapeutic ultrasound in men and women aged 20 to 70 years with knee osteoarthritis. The most consistent outcomes were pain reduction and functional improvement (WOMAC, Lequesne index); combining ultrasound with exercise was superior to isolated application. Parameter heterogeneity still limits conclusions about the optimal protocol.

Key words:-

Therapeutic ultrasound, Knee osteoarthritis, Physical therapy, Phonophoresis, Randomized controlled trial

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Introduction:-

Knee osteoarthritis (OA) is a degenerative and progressive joint disease characterized by deterioration of the hyaline cartilage, subchondral bone remodeling, and low-grade synovial inflammation, resulting in pain, stiffness, reduced range of motion, and functional impairment. It is one of the leading causes of musculoskeletal disability among middle-aged and older adults, with substantial socioeconomic impact arising from work absenteeism, healthcare utilization, and the eventual need for total knee arthroplasty.

Among the electrophysical agents used in musculoskeletal physical therapy, therapeutic ultrasound (TUS) holds a historically prominent position, being applied in both continuous and pulsed modes for analgesic, anti-inflammatory, and tissue-repair purposes. Over the past decades, the development of variants such as low-intensity pulsed ultrasound (LIPUS), phonophoresis (the use of ultrasound to enhance transdermal drug delivery), and, more recently, low-intensity focused ultrasound for neuromodulation has broadened the clinical applications of this technology in knee osteoarthritis (ABED et al., 2024; ILFELD et al., 2025). Recent studies have also explored combining ultrasound with other physical therapy interventions, such as therapeutic exercise and extracorporeal shockwave therapy, seeking synergistic effects on pain and joint function (YANG et al., 2025; KHADOUR; KHADOUR; ALHARBI, 2025).

Despite its widespread use, the literature on the effectiveness of therapeutic ultrasound in knee OA is still marked by considerable methodological heterogeneity regarding application parameters (frequency, intensity, duty cycle, exposure time), whether or not it is combined with other interventions (exercise, electrotherapy, laser therapy, shockwave therapy), and the outcome instruments used (ATAN et al., 2024; CP et al., 2024; SHARMA et al., 2025). This dispersion hinders the derivation of uniform clinical recommendations and justifies periodic reviews that update the evidence landscape, particularly given the growing output of randomized controlled trials in recent years.

Beyond the analgesic and functional effects classically attributed to therapeutic ultrasound, recent mechanistic investigations have demonstrated its impact on the biomechanical properties of periarticular tissues, such as the stiffness and gliding of the infrapatellar fat pad, a structure

implicated in anterior knee pain (IKEDA et al., 2024; IKEDA et al., 2026), as well as on inflammatory biochemical markers in the synovial fluid when combined with other physical modalities (KHADOUR; KHADOUR; ALHARBI, 2025). These findings reinforce the biological plausibility of the observed clinical effects and justify a systematic update of the evidence on this topic.

This integrative review was designed to address the following guiding question: what is the effectiveness of therapeutic ultrasound, across its different modalities, on pain and function outcomes in men and women aged 20 to 70 years with knee osteoarthritis, according to randomized controlled trials published between 2020 and 2026?

Objective:-

To synthesize and critically analyze the evidence available from randomized controlled trials, published between 2020 and 2026, on the application of therapeutic ultrasound — in its continuous, low-intensity pulsed, phonophoretic, and focused modalities — in the conservative management of knee osteoarthritis in adults aged 20 to 70 years, identifying application protocols, assessed outcomes, observed clinical effects, and methodological gaps in the current literature.

Methodology:-

Study design

This is an integrative literature review, a method that allows the incorporation of studies with different designs to provide a broad understanding of the phenomenon under investigation, following the following steps: (1) identification of the research question; (2) definition of inclusion and exclusion criteria and literature search; (3) categorization of studies; (4) evaluation of the included studies; (5) interpretation of results; and (6) synthesis of knowledge.

PICO strategy

To structure the research question and guide the search strategy, the PICO framework was adopted, a strategy widely used in health literature reviews to break down the clinical question into its constituent elements:

P (Population): men and women aged 20 to 70 years with a clinical and/or radiographic diagnosis of knee osteoarthritis;

I (Intervention): application of therapeutic ultrasound, in its continuous, low-intensity pulsed (LIPUS), phonophoretic, or low-intensity focused modalities, alone or combined with other physical therapy interventions;

C (Comparison): no intervention, sham procedure, placebo, or other isolated therapeutic modalities (therapeutic exercise, laser therapy, extracorporeal shockwave therapy, among others);

O (Outcomes): pain reduction (Visual Analogue Scale – VAS, Numerical Rating Scale – NRS, algometry) and functional improvement (WOMAC, Lequesne index, range of motion, gait parameters), in addition to secondary biomechanical and biochemical outcomes, when available.

To these four elements, the study design (S) was added as a complementary component, restricted to randomized controlled trials, forming the PICOS strategy that underpinned both the construction of the search terms and the eligibility criteria detailed below.

Search strategy

The search was conducted in the PubMed/MEDLINE, SciELO, Google Scholar, and PEDro (Physiotherapy Evidence Database) databases, using English and Portuguese descriptors combined with Boolean operators AND/OR: "therapeutic ultrasound" OR "low-intensity pulsed ultrasound" OR "phonophoresis" AND "knee osteoarthritis" AND "randomized controlled trial", and their Portuguese equivalents. In the PEDro database, priority was given to the "clinical trial" design filter and to searching the body part/structure "knee" combined with the term "ultrasound".

Eligibility criteria

Studies were included if they met the following criteria: (a) randomized controlled trial design; (b) publication between January 2020 and 2026; (c) sample composed of men and women aged 20 to 70 years with a clinical and/or radiographic diagnosis of knee osteoarthritis; (d) use of therapeutic ultrasound (continuous, pulsed, phonophoretic, or focused) as an isolated intervention or combined with another resource; (e) assessment of pain and/or function outcomes. Studies were excluded if their samples fell exclusively outside the established age range, as well as systematic reviews, preclinical studies, research protocols without published results, and studies in which ultrasound use was restricted to diagnostic purposes or guidance for invasive procedures (e.g., ultrasound-guided genicular nerve blocks), since these do not represent a therapeutic application of the resource.

Data extraction and synthesis

From the selected studies, the following information was extracted: authorship and year of publication, design and sample size, characteristics of the ultrasound intervention (physical parameters, association with other techniques, treatment frequency and duration), outcome instruments used (Visual Analogue Scale – VAS, Western Ontario and McMaster Universities Osteoarthritis Index – WOMAC, Lequesne index, among others), and main findings. Data were organized into a summary table and analyzed narratively, grouping studies by the type of ultrasound modality employed.

Results:-

The search identified a set of randomized controlled trials published between 2024 and 2026 that met the eligibility criteria, encompassing different modalities of therapeutic ultrasound applied to knee osteoarthritis: conventional continuous ultrasound used as part of baseline physical therapy

protocols, low-intensity pulsed ultrasound (LIPUS), drug phonophoresis, and low-intensity focused ultrasound for neuromodulation. Table 1 summarizes the main characteristics and findings of the included studies.

Table 1 – Summary of randomized controlled trials on therapeutic ultrasound in knee osteoarthritis (2020–2026)

Author/Year	Design and sample	Ultrasound intervention	Main outcomes	DOI (suffix)
Abed et al. (2024)	RCT, n=78, mild-to-moderate unilateral chronic KOA	Metformin 1.2% phonophoresis + exercise vs. phonophoresis alone vs. conventional therapeutic US (neutral gel), 3x/week, 4 weeks	All groups improved on VAS, WOMAC and ROM; the exercise-combined group was superior to the other conditions ($p<0.05$)	s13018-024-05120-0
Yang et al. (2025)	RCT, KOA, 3 parallel groups	LIPUS alone vs. aerobic exercise (AE) vs. LIPUS+AE, 12 weeks	LIPUS+AE was superior to LIPUS or AE alone in VAS, Lequesne index and gait parameters	MD.0000000000043343
Khadour; Khadour; Alharbi (2025)	RCT, n=220 (110/group), KOA	LIPUS 1 MHz/0.5 W/cm² + shockwave therapy (LESWT) vs. shockwave therapy alone (R-ESWT)	LESWT was superior in clinical effectiveness, WOMAC, VAS, ROM; reduced IL-1β, TNF-α, MMP-3	s13018-025-06384-w
Ilfeld et al. (2025)	Pilot RCT, masked, sham-controlled	Low-intensity focused ultrasound (neuromodulation) targeting knee structures	Feasibility study; potential analgesic effect via reversible nerve conduction block, no relevant adverse events	10.1002/jum.16706
Sharma et al. (2025)	RCT, n=116, 45–70 years, mountainous terrain population	Ibuprofen gel phonophoresis (IGP) vs. high-intensity laser therapy (HILT) + exercise, 3 weeks	Both reduced pain and improved WOMAC/SF-36; HILT showed a slightly greater gain	s10103-025-04613-6
Atan et al. (2024)	RCT, n=30 women, moderate-to-severe KOA	Therapeutic US + TENS + hot pack in all groups; anti-gravity treadmill vs. traditional treadmill vs. control, 8 weeks	The anti-gravity group showed greater pain reduction and functional improvement; the traditional treadmill reduced femoral cartilage thickness	s11845-024-03836-w
Cp et al. (2024)	RCT, n=30, grade IV KOA (Kellgren-Lawrence)	Conventional physiotherapy (US + isometric strengthening) vs. same baseline treatment + shockwave therapy, 4 weeks	Both improved LEFS scores; adding shockwave therapy increased the gain (81.9% vs. 48.1%)	s41598-024-67511-x
Ikeda et al. (2024)	Crossover RCT, double-blind (sham), n=24, healthy	HICUS 1 MHz/2.5 W/cm², 100% duty cycle, 5 min, over the infrapatellar fat pad	Reduced stiffness and improved fat pad gliding at 10° of flexion, effect sustained for 15 min	ultrasmedbio.2024.09.006
Ikeda et al. (2026)	Crossover RCT, double-blind (sham), n=20, healthy	HICUS combined with active knee exercise, same protocol as the previous study	Exercise + HICUS enhanced the reduction in fat pad stiffness across different flexion angles	jbiomech.2026.113191
Kamal et al. (2025)	RCT, n=130, ≥65 years, bilateral KOA	Therapeutic US within a conventional protocol (electrotherapy, TENS, laser) vs. a program with additional gait training	Gait training showed superior functional gains; ultrasound was used only for baseline characterization	medicina61122118

Source: prepared by the author (2026), based on data retrieved from PubMed. Note: the "DOI (suffix)" column shows the final part of the identifier; the complete DOI for each study is provided in the reference list.

Conventional therapeutic ultrasound combined with multimodal protocols

In several studies, continuous therapeutic ultrasound appeared as a baseline component of conventional physical therapy protocols, generally combined with electrotherapy (TENS), superficial thermotherapy, and kinesiotherapy, serving as a comparator or standard treatment against more recent interventions. Atan et al. (2024) compared anti-gravity treadmill training with traditional treadmill training, both combined with hot packs, TENS, and therapeutic ultrasound, observing a significant reduction in pain in both the intervention and control groups, with a more pronounced functional improvement in the anti-gravity treadmill group, whereas

traditional treadmill training was associated with reduced femoral cartilage thickness. Similarly, Cp et al. (2024) used therapeutic ultrasound as part of conventional physiotherapy in patients with grade IV osteoarthritis, finding significant functional improvement in both the conventional physiotherapy group alone and the group that additionally received extracorporeal shockwave therapy, with a greater gain in the latter.

Low-intensity pulsed ultrasound (LIPUS)

LIPUS was investigated both alone and in combination with aerobic exercise or extracorporeal shockwave therapy. Yang et al. (2025) demonstrated that combining LIPUS with aerobic exercise produced greater gains in pain, Lequesne index, and gait kinematic parameters compared with each intervention alone, suggesting a synergistic effect between the electrophysical agent and voluntary mechanical stimulation. Khadour, Khadour, and Alharbi (2025) compared LIPUS combined with radial extracorporeal shockwave therapy (LESWT) with shockwave therapy alone, finding a higher clinical effectiveness rate in the combined group, accompanied by a more pronounced reduction in synovial fluid inflammatory markers (interleukin-1β, tumor necrosis factor-α, and metalloproteinase-3), which provides evidence of a biochemical mechanism underlying the observed clinical effect.

Phonophoresis

Phonophoresis, a technique that uses ultrasound to deliver drugs transdermally, was evaluated in two relevant studies. Abed et al. (2024) compared metformin phonophoresis combined with therapeutic exercise, phonophoresis alone, and conventional therapeutic ultrasound (neutral gel), finding significant improvement in all groups after four weeks, but with statistically significant superiority in the group that combined phonophoresis with exercise across all assessed outcomes (pain, range of motion, and function). Sharma et al. (2025) compared ibuprofen gel phonophoresis with Class IV high-intensity laser therapy in a population living in mountainous terrain, finding significant improvement in pain and function in both groups, with a slight advantage for laser therapy, positioning phonophoresis as a therapeutic alternative comparable to more recent resources, although not superior.

Low-intensity focused ultrasound (neuromodulation)

A more recent line of investigation concerns the use of low-intensity focused ultrasound as a non-invasive neuromodulation technique, with the potential for reversible blockade of peripheral nerve conduction, analogous to a local anesthetic block. Ilfeld et al. (2025) conducted a randomized, masked, sham-controlled pilot study aimed at assessing the feasibility and safety of this technique in patients with knee osteoarthritis pain, with no relevant complications reported, indicating that this is an emerging line of research that still requires larger-scale efficacy trials.

Mechanistic studies in healthy participants

Two studies conducted by Ikeda et al. (2024; 2026), although carried out in healthy volunteers rather than specifically in patients with knee osteoarthritis, were considered relevant for

understanding the biomechanical mechanisms of therapeutic ultrasound, as they demonstrated that high-intensity continuous ultrasound (HICUS), alone or combined with active knee exercise, reduces stiffness and improves gliding of the infrapatellar fat pad, a structure frequently implicated in anterior knee pain and potentially relevant to the pathophysiology of osteoarthritis.

Discussion:-

The synthesis of the included studies indicates that therapeutic ultrasound, across its different modalities, has a favorable and consistent effect on pain and function in patients with knee osteoarthritis, corroborating the historical role of this resource in physical therapy practice. However, a recurring finding stands out: combining ultrasound with active interventions — particularly therapeutic exercise — produces greater gains than its isolated application (ABED et al., 2024; YANG et al., 2025), which is consistent with international osteoarthritis management guidelines that position therapeutic exercise as a first-line intervention and electrophysical agents as adjuncts.

From the standpoint of mechanisms of action, the findings by Khadour, Khadour, and Alharbi (2025) regarding the reduction of synovial inflammatory markers after LIPUS combined with shockwave therapy, as well as the biomechanical studies by Ikeda et al. (2024; 2026) on the reduction of infrapatellar fat pad stiffness, provide biological plausibility for the observed clinical effects, suggesting that therapeutic ultrasound acts not only through symptomatic modulation but also through interference with inflammatory processes and the mechanical properties of periarticular tissues.

The emergence of low-intensity focused ultrasound as a neuromodulation strategy (ILFELD et al., 2025) represents a promising direction, still in an early stage of clinical investigation, that broadens the rationale for ultrasound use beyond its classic thermal and mechanical effects, bringing it closer to non-invasive interventional techniques for chronic joint pain control.

Among the limitations identified in the analyzed literature, the following stand out: (a) substantial heterogeneity in the physical parameters of ultrasound application (frequency, intensity, duty cycle, exposure time), which hinders direct comparison between studies and the definition of an optimal protocol; (b) a predominance of small samples and single-center designs, limiting the generalizability of findings; (c) variability in the outcome instruments used, although the Visual Analogue Scale and WOMAC are the most recurrent; (d) a scarcity of studies isolating the specific effect of therapeutic ultrasound without simultaneous association with other interventions, hindering causal attribution of the observed effects; and (e) sample age ranges not always matching the 20-to-70-year range adopted in this review, with a predominance of middle-aged and older participants, reflecting the epidemiological profile of knee osteoarthritis.

Additionally, it was observed that a considerable share of recent scientific output on “ultrasound” and knee osteoarthritis refers to the use of ultrasound as an imaging tool to guide invasive procedures (genicular nerve blocks, chemical neurolysis, intra-articular injections), rather than as

an electrophysical therapeutic resource per se. Such studies were deliberately excluded from this review, as they did not correspond to the proposed object of investigation, although their frequency in the literature signals a trend toward shifting the clinical use of ultrasound from direct therapeutic application toward guidance for minimally invasive interventions.

Conclusion:-

The evidence available from randomized controlled trials published between 2020 and 2026 indicates that therapeutic ultrasound — in its continuous, low-intensity pulsed, and phonophoretic modalities — exerts a favorable analgesic and functional effect in adults aged 20 to 70 years with knee osteoarthritis, an effect that is enhanced when the resource is combined with therapeutic exercise programs. Low-intensity focused ultrasound emerges as a promising neuromodulation strategy, still lacking larger-scale efficacy studies. Future clinical trials should standardize therapeutic ultrasound application parameters, adopt designs that allow isolation of its specific effect, and use comparable outcome instruments, in order to support more robust clinical recommendations and optimized application protocols for physical therapy practice.

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